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Editorial Comment

Vasospastic Angina: A Continuing Search for Mechanism(s)*

GOTTLIEB C. FRIESINGER, MD, FACC,
ROSE MARIE ROBERTSON, MD, FACC

Nashville, Tennessee

It is appealing to believe that better understanding of the specific pathophysiology of a disease entity allows the design or selection of more specific and better therapy. In many instances, however, it is obvious that empiric or nonspecific therapy, or both, is very effective, irrespective of our understanding of pathophysiologic mechanisms. Vasospastic angina is such an instance, since therapy utilizing nitrates and calcium channel blocking agents, with their potent action on vascular smooth muscle, is usually effective. Our understanding of the pathophysiology of this disorder continues to lag behind therapeutic advances and, insofar as it has progressed, has done so largely through negative trials.

The report by Yui et al. (1) in this issue of JACC addresses the hypothesis that thromboxane A_2 is causal in vasospastic angina. Previous studies (2–5) attempting to answer this question have utilized a variety of methods. These have included both intravenous and coronary sinus sampling of thromboxane B_2 and therapeutic trials using moderate-dose aspirin as a nonspecific cyclooxygenase inhibitor (4,5). The effectiveness of aspirin in inhibiting thromboxane A_2 production has been defined by demonstrating a decrease in urinary 2,3-dinor thromboxane B_2 excretion (4). These studies have suggested that thromboxane A_2 is unimportant in initiating vasospastic angina. The hypothesis that a thromboxane A_2-prostacyclin "imbalance" may play an essential role has been difficult to dispel despite evidence that prostacyclin infusion is ineffective in most patients with vasospastic angina (6).

Methodologic issues. In the study of Yui et al., a well designed experimental protocol was used to evaluate patients with clearly documented vasospastic angina. The use of a placebo-controlled design allows for easier interpretation of the therapeutic results and is a strong study feature. On the other hand, the difficulties in interpreting biochemical data purporting to implicate prostanoids in this clinical syndrome are substantial. These relate both to the inherent characteristics of the system being monitored and to the methods available for measurement, with this combination resulting in a Heisenberg-like effect. To determine the contribution of a potential mediator of coronary spasm, it would be desirable to measure the mediator near the active site in the coronary circulation, that is, in the coronary artery, to avoid dilutional effects and artifacts. With current methods the coronary sinus is the closest practical site, and blood must be sampled through long catheters; this invariably results in some activation of platelets. The capacity to generate thromboxane B_2 in serum is approximately 300 to 400 ng/ml, so that activation of platelets to less than 0.1% of their capacity during catheter passage would account for virtually all of the baseline endogenous thromboxane B_2 levels found in the studies described here. A closer estimate of endogenous thromboxane B_2 plasma concentration would probably be about 1 to 2 pg/ml (7). Even allowing for the artifactual elevation produced by sampling and despite the increase in thromboxane B_2 during ischemic attacks, these high baseline levels make thromboxane data difficult to interpret. As Yui et al. point out, an increase in thromboxane B_2 with ischemia does not establish a causal role. The potential difficulties in defining pathophysiologic mechanisms by studying induced rather than spontaneous episodes of vasospastic angina should also be appreciated.

Additional problems in evaluating therapeutic trials. Thromboxane A_2 might contribute to coronary vasospasm in at least two ways. It is a potent vasoconstrictor, and its presence might potentiate epicardial or arteriolar vasoconstriction. In addition, thromboxane-dependent platelet activation might compromise coronary flow in and of itself. There is evidence both in vitro and ex vivo that only 5 to 10% of the normal capacity to generate thromboxane A_2 is needed to sustain thromboxane-dependent platelet activation (8,9). If one assumes that the levels of plasma thromboxane B_2 described in this report are not endogenous baseline levels but rather a measure of the capacity to produce thromboxane, it would appear that OKY-046, the specific thromboxane synthase inhibitor utilized, inhibited thromboxane A_2 formation by 75 to 80%. Thus, thromboxane-dependent platelet activation might be expected to continue. Although a higher dose of OKY-046 might further decrease the capacity for production of thromboxane B_2, the lack of therapeutic effect seen in studies employing prostacyclin infusions may have answered this question for most patients with coronary spasm. A subset of patients for whom manipulation of prostanoids could be important may still exist. Although specific thromboxane synthase inhibition does appear to increase prostacyclin production, as with throm-

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From the Vanderbilt University School of Medicine, Division of Cardiology, Nashville, Tennessee.

Address for reprints: Gottlieb C. Friesinger, MD, Division of Cardiology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232.

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boxane B_2 there are important disadvantages associated with the measurement of serum 6-keto-prostaglandin $F_{1\alpha}$ by radioimmunoassay, even utilizing highly sensitive and specific antibodies (9). The authors avoided one potential problem, the elevation of prostaglandin I_2 production due to intravenous or intraarterial catheter placement (11), by not utilizing samples collected at catheterization for these studies.

Research implications. Despite difficulties inherent in exploring the mechanism or mechanisms in vasospastic angina, this report confirms and extends observations suggesting that thromboxane A_2 is not likely to be responsible for the initiation of ischemic episodes in this syndrome. Multiple studies during the past decade have approached the problem of coronary vasospasm by attempting to find a specific mediator that could explain this clinical syndrome. There is now a sizable body of data suggesting that this approach, which seemed so rational, may need modification. The responsiveness of coronary arteries in patients with variant angina to multiple provocative stimuli and the focal nature of coronary spasm suggest that a segmental abnormality of the coronary vasculature causes a heightened sensitivity. Several animal models (12,13) suggest that this abnormality is in all probability related to the development of atherosclerosis. The role of endothelial injury or dysfunction, or both, in this process may be pivotal. It is clear that the endothelium is an extraordinarily active and complex tissue, and its role in altering the effect of vasoactive agents is currently being defined (14,15). The particular stimulus-producing spasm in any given patient may vary from time to time and it is possible that multiple circulating or locally produced mediators, possibly interacting with or modulated by the presence or absence of one or more endothelial factors, are important. Although further clinical studies with specific inhibitors may provide useful information, it is likely that the essential pieces of this puzzle will come from a more basic understanding of the pathophysiology of these "hyperreactive" arterial segments.

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